General

Guideline Title

Somatostatin analogues for the management of neuroendocrine tumours.

Bibliographic Source(s)

Alberta Provincial Endocrine Tumour Team. Somatostatin analogues for the management of neuroendocrine tumours. Edmonton (AB): CancerControl Alberta; 2015 Mar. 19 p. (Clinical practice guideline; no. ENDO-003). [50 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Endocrine Tumour Team. Octreotide for the management of neuroendocrine tumours. Edmonton (Alberta): CancerControl Alberta; 2013 Nov. 16 p. (Clinical practice guideline; no. ENDO-003). [46 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Described below are possible indications for the use of somatostatin analogues in neuroendocrine tumours (NETs).

1. Management of Symptomatic Secretory Syndromes
    - Somatostatin analogues are recommended for symptom control in patients with secretory syndromes resulting from carcinoid syndrome and gastrinomas, insulinomas, somatostatinomas, glucagonomas and VIPomas with locoregional and metastatic disease.
        - Octreotide dosing for symptom control: A trial of octreotide 100–250 mcg subcutaneously (SC) three times a day (TID) for 1–2 weeks followed by introduction of octreotide LAR 20–30 mg intramuscular (IM) every 4 weeks. (Note: LAR is a long-acting formulation of octreotide acetate injection.)
        - Dose and frequency may be increased for symptom control, as needed.
        - Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.
        - Lanreotide dosing for symptom control:
            - Somatuline LA 30 mg IM every 10–14 days[1]
            - Somatuline Autogel 60–120 mg SC every 28 days[2]
2. Tumour Control
    - Octreotide LAR has been shown in the PROMID study to slow tumour progression, as compared to placebo, in patients with locoregional unresectable or metastatic well-differentiated (low grade) NETs of mid-gut origin and those of unknown origin believed

to be a mid-gut primary. Therefore, octreotide LAR should be considered for its anti-tumour effect in patients with locoregional unresectable or metastatic well-differentiated (low grade) mid-gut NETs whose disease is progressing regardless of functional status of the tumour.
    - Octreotide LAR dosing for tumour control: 30 mg IM every 4 weeks. Note: therapeutic levels of octreotide would not be expected to be reached for 10–14 days after LAR injection.
- Octreotide has not been compared to placebo in the phase III setting in patients with poorly differentiated mid-gut NETs or other NETs (i.e., non-mid-gut primaries) with locoregional unresectable disease or distant metastases.
- Lanreotide has been shown in the CLARINET study to slow prolong progression-free survival in comparison to placebo in patients with advanced well to moderately differentiated, nonfunctioning somatostatin receptor positive neuroendocrine tumours.
    - Lanreotide dosing for tumour control: 120 mg SC injection every 28 days

3. Management of Carcinoid Heart Disease
    - Octreotide is used to treat carcinoid crises.
        - Octreotide dosing for carcinoid heart disease: bolus of 100–500 mcg intravenous (IV) or by infusion; urgent situations may require high doses and up to 54,000 mcg has been reported.
    - There is a paucity of data on the use of octreotide for the prevention of carcinoid heart disease in patients with carcinoid tumours. However, given the life-threatening nature of carcinoid heart disease and the relative safety of octreotide, use of octreotide should be considered in this setting.
        - Patients with 5-hydroxyindoleacetic acid (5-HIAA) levels greater than 50 mg/24 hours should be considered for octreotide therapy, with the goal of normalizing 5-HIAA 24-hour urine excretion, if possible.
        - Dosing for the prevention of carcinoid heart disease: octreotide LAR 20–30 mg IV every 4 weeks.
4. Management of Symptoms Secondary to Elevated Calcitonin in Medullary Thyroid Carcinoma
    - Octreotide has been shown to relieve symptoms associated with elevated calcitonin levels in patients with medullary thyroid carcinoma. Therefore, octreotide is recommended to manage symptoms (i.e., diarrhea) in patients with elevated calcitonin levels in medullary thyroid carcinoma.
        - Octreotide dosing for symptoms associated with metastatic medullary thyroid cancer: A trial of daily octreotide 100–250 mcg TID SC for 1–2 weeks with subsequent introduction of monthly octreotide LAR at a dose of 20–30 mg IM every 4 weeks. Octreotide can be given long-term without significant adverse effects.

[1]eMC. Somatuline LA [Summary of Product Characteristics]. 2014; Available at: https://www.medicines.org.uk/emc/medicine/877 .

[2]eCPS. Somatuline® Autogel® [Drug Monograph]. 2012. [Accessed 2015 Mar 18]. Available at: https://www.e-therapeutics.ca.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Neuroendocrine tumours (NETs)

Guideline Category

Management

Treatment

Clinical Specialty

Endocrinology

Oncology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide evidence-based recommendations on the use of somatostatin analogues for neuroendocrine tumours (NETs) and to define which patients are candidates for treatment with these agents

Target Population

Patients diagnosed with neuroendocrine tumours (NETs) of the gastrointestinal tract, pancreas, lungs, thyroid, parathyroid, adrenal glands, and pituitary gland, and NETs of unknown origin

Interventions and Practices Considered

Somatostatin analogues (octreotide and lanreotide) in appropriate dosing for:

- Symptom control in patients with secretory syndromes
- Tumour control
- Management of carcinoid heart disease
- Relieving symptoms associated with elevated calcitonin levels (medullary thyroid carcinoma)

Major Outcomes Considered

- Symptom control (e.g., reduction in diarrhea, changes in 5-hydroxyindoleacetic acid [5-HIAA] and chromogranin A [CgA] levels, stool frequency, flushing episodes)
- Tumour control (progression-free and overall survival rates)
- Serum calcitonin levels
- Adverse events

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (Patient or Population, Intervention, Comparisons, Outcomes).

Guideline Questions

- Are somatostatin analogues effective for symptom management in secretory syndromes resulting from neuroendocrine tumours (NETs)? If so, for which patients and what are the appropriate dosing regimens?
- Are somatostatin analogues effective in delaying tumour progression among patients with NETs? If so, for which patients and what are the appropriate dosing regimens?
- Are somatostatin analogues effective for the management of carcinoid heart disease? If so, for which patients and what are the appropriate dosing regimens?
- Is octreotide effective for the management of symptoms secondary to elevated calcitonin in medullary thyroid carcinoma? If so, for which patients and what is the appropriate dosing regimen?

Search Strategy

The PubMED database was searched (1965 through 2013 May) for relevant publications using the following search terms: *octreotide* AND *neuroendocrine tumour*. Results were limited to randomized controlled trials and phase II-III clinical trials. Thirty-eight citations were returned in PubMed. Excluded from these were retrospective studies, case studies, studies published before 2001, and those that did not report response or survival outcomes, leaving a total of ten studies. The American Society of Clinical Oncology (ASCO) meeting abstracts database was searched (2009 through 2012 March) for relevant abstracts; five abstracts (phase III trials) were identified.

Additional searches were conducted of the PubMED database for studies on the use of octreotide for carcinoid heart disease, malignant bowel obstruction, and increased calcitonin levels in medullary thyroid carcinoma. The searches included studies involving patients with any type malignancy (i.e., not limited to NETs). The key words *octreotide* AND *carcinoid heart disease* or *malignant bowel obstruction* or *calcitonin* were used.

For the 2014 update of the guideline the PubMED, MEDLINE and EMBASE databases were searched (2013 through 2014 October) for relevant publications using the following search terms: *octreotide* AND *neuroendocrine tumour*. In addition, the databases were searched (2009 through 2014 October) for relevant publications using the following search terms: *lanreotide* AND *neuroendocrine tumour*. A total of five additional studies were relevant and are summarized in the tables in Appendix B in the original guideline document.

Number of Source Documents

The 2014 update identified 298 studies, of which 5 were relevant and are summarized in Appendix B in the original guideline document.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Cutaneous Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the GURU Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Evidence to inform the recommendations on tumour control and symptom management is summarized in the tables in Appendix B in the original guideline document.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Endocrine Tumour Team. Members of the Alberta Provincial Endocrine Tumour Team include medical oncologists, endocrinologists, surgeons, and nurses. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Endocrine Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the GURU Handbook (see the "Availability of Companion Documents" field).

Formulating Recommendations

The working group members formulated the guideline recommendations based on the evidence synthesized by the KM Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the GURU Handbook (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the GURU does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Endocrine Tumour Team.

Guideline Review and Approval

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it is officially endorsed by the Provincial Tumour Team Lead and the Director of Provincial Clinical Teams.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Octreotide and lanreotide have been shown to improve symptoms associated with hypersecretory syndromes in patients with neuroendocrine tumours (NETs).
- Octreotide LAR has been shown to slow tumour progression, as compared to placebo, in patients with locoregional unresectable or metastatic well-differentiated (low grade) NETs. (Note: LAR is a long-acting formulation of octreotide acetate injection.)
- Octreotide normalizes 5-hydroxyindoleacetic acid (5-HIAA) levels, which at levels greater than 50 mg/24 hours are associated with an increased risk of developing carcinoid heart disease.
- Octreotide has been shown to relieve symptoms associated with elevated calcitonin levels in patients with medullary thyroid carcinoma.

Potential Harms

- The use of octreotide in the prophylactic setting is controversial because there is a paucity of data on its use in patients with carcinoid tumours in this setting. Canadian consensus guidelines recommend that early intervention with octreotide should be considered, given that toxicity is low and the morbidity and mortality rates associated with carcinoid heart disease are high.
- Refer to Appendix B in the original guideline document for adverse events of various treatments reported in the literature.

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Endocrine Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services Web site.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

Implementation Tools

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Mar

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

Guideline Committee

Alberta Provincial Endocrine Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Endocrine Tumour Team include medical oncologists, endocrinologists, surgeons, and nurses.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Endocrine Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Endocrine Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However, the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

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This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Alberta Health Services Web site.

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Version 2. Edmonton (AB): CancerControl Alberta; 2013 Jan. 5 p. Electronic copies: Available from the Alberta Health Services Web site.

In addition, the American Joint Committee on Cancer (AJCC) (7th Edition) staging for neuroendocrine tumours is available in Appendix A of the original guideline document.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 12, 2014. The information was verified by the guideline developer on September 22, 2014. This summary was updated by ECRI Institute on March 14, 2016. The updated information was verified by the guideline developer on April 4, 2016.

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